Therapeutic methods and compositions for the treatment of impaired interpersonal and behavioral disorders.

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of application No. PCT/EP00/06259 filed on June 22, 2000, now abandoned.

Field of the invention

The invention relates to the field of psychopharmacology. More particularly, the invention relates to the treatment of DSM-III disorders, such as impaired interpersonal and behavioral disorders.

Summary of the related art

The field of psychopharmacology has produced numerous breakthroughs in behavioral modification since the 1950s, when phenothiazines were first introduced. Unfortunately, certain types of mental disorders have proven refractory to pharmacotherapy. Among these refractory disorders are disorders designated DSM-III (see Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Assoc., 1992), which are characterized by impaired interpersonal interactions and other behavioral defects. These defects include impairment in communication, impairment of interpersonal activities, restricted reprotoire of interest, fear of partners, decreased awareness of partners similar to that seen in autism, attention deficit disorder, impairment in social functioning, solitary conduct disorders, decreased ability to relate to others, avoidance disorders, unassertive states, reactive attachment disorders, lack of social interest, impaired interpersonal functioning and relationship to the external world, impairment of self-care, decreased interest in environment, hypersomnia, and adjustment disorders with impairment in occupational functioning.

Also included in these disorders are sexual defects, including arousal disorders, impaired sexual behavior in the form of a lack of affective attention, and impaired social activity linked to sexuality. These latter disorders can manifest in part as a condition known as male erectile dysfunction (M.E.D.), a serious condition believed to affect some 8% of males worldwide. In

addition, hypoactive sexual desire disorder (H.S.D.D.) is believed to affect 20% of the population worldwide, with no available therapy. Most efforts to treat M.E.D. have vasodilators to induce erection, rather than utilizing behavior modifiers. For example, PDE5 inhibitors, such as sildenafil, alpha blocking agents, such as moxysylate or phentolamine, and prostaglandins have been used. Unfortunately, these treatments suffer from certain deficiencies. The PDE5 inhibitors, for example, are subject to degradation via the cytochrome P450 degradation pathway. Prostaglandins require unpleasant intracavernous or intra-urethral administration. In addition, none of these treatments directly affects the emotional, affectionate aspects of the sexual relationship.

There is, therefore, a need for new therapeutic compositions and methods for treating DSM-III disorders, including M.E.D. and H.S.D.D. Ideally, such compositions and methods should provide improved awareness and alertness to environment, improved adaptation to environment and ability to sustain attention, and increased interest in environment and capacity for arousal, without increased aggressiveness.

Many central peptides, known as neuropeptides, have effects on behavior. For example, Mondal *et al.*, B.B.R.C. 256: 495-499 (1999) teaches that the neuropeptide orexin can be used to treat eating disorders. Insel *et al.*, Reviews of Reproduction 2: 28-37 (1997) discloses that oxytocin, a neurohypohyseal peptide can influence reproductive behavior. Unfortunately, oxytocin can produce unwanted side effects in male subjects. For example, Uvnaes-Moberg *et al.*, Pharmacology, Biochemistry and Behavior 49: 101-106 (1994) teaches that high doses of oxytocin decrease locomotion and low doses of oxytocin cause an anxiolytic-like effect in male rats. Thus, neuropeptides have shown limitations as therapeutics for DSM-III disorders, particularly for sexual disorders.

Rosinski-Chupin *et al.* U.S. Patent No. 5,859,189 (1999) discloses a purified pentapeptide or tetrapeptide expressed in the submaxillary gland of the rat, and suggests that it may fulfil an important function specific for the male. However, Rougeot *et al.*, Amer. J. Physiol. 273: R1309-R1320 (1997) discloses biodistribution for this peptide with autoradiographs which suggest that the peptide does not cross the blood brain barrier. Thus, this peptide would not be expected to be a promising candidate for behavior modification.

BRIEF SUMMARY OF THE INVENTION

The invention provides new therapeutic compositions and methods for treating DSM-III disorders, including M.E.D. The compositions and methods according to the invention provide improved awareness and alertness to environment, improved adaptation to environment and ability to sustain attention, and increased interest in environment and capacity for arousal, without increased aggressiveness.

The present inventor has surprisingly discovered that peptides of the type disclosed in U.S. Patent No. 5,859,189 are effective as therapeutics for DSM-III disorders, including without limitation sexual disorders.

In a first aspect, the invention provides methods for treating DSM-III disorders. The methods according to the invention comprise administering to a mammal having a DSM-III disorder an amount of a peptide or a peptidomimetic according to the invention that is sufficient to reduce or eliminate symptoms of the DSM-III disorder.

In certain preferred embodiments, the DSM-III disorder is an avoidance disorder. In certain preferred embodiments, the DSM-III disorder is a decreased awareness disorder. In certain preferred embodiments, the DSM-III disorder is an attention deficit disorder. In certain preferred embodiments, the DSM-III disorder is an arousal disorder. In certain preferred embodiments, the DSM-III disorder is impaired interpersonal functioning and relationship to the external world. In certain preferred embodiments, the DSM-III disorder is impaired social activity linked to sexuality. In certain preferred embodiments, the DSM-III disorder is impaired sexual behavior. In certain preferred embodiments, the DSM-III disorder comprises symptoms of more than one of these disorders.

In certain preferred embodiments, the peptide or peptidomimetic according to the invention is administered together with a second pharmaceutical, wherein the second pharmaceutical agent is present in an amount insufficient to reduce or eliminate symptoms of the DSM-III disorder, and wherein the peptide or peptidomimetic according to the invention and the second pharmaceutical agent act synergistically to reduce or eliminate symptoms of the DSM-III disorder.

In a second aspect, the invention provides therapeutic compositions comprising a peptide or peptidomimetic according to the invention in an amount sufficient to reduce or eliminate

symptoms of a DSM-III disorder in a mammal having the DSM-III disorder, and further comprising a pharmaceutically acceptable diluent and/or buffer and/or excipient.

In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of an avoidance disorder. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of a decreased awareness disorder. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of an attention deficit disorder. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of an arousal disorder. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of impaired interpersonal functioning and relationship to the external world. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of impaired social activity linked to sexuality. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of impaired sexual behavior. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of symptoms of more than one of these disorders.

In certain preferred embodiments, the peptide or peptidomimetic according to the invention is present in the therapeutic composition according to the invention together with a second pharmaceutical, wherein the second pharmaceutical agent is present in an amount insufficient to reduce or eliminate symptoms of the DSM-III disorder, and wherein the peptide or peptidomimetic according to the invention and the second pharmaceutical agent act synergistically to reduce or eliminate symptoms of the DSM-III disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows sleep results in an Irwin test on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 2 shows results of a startle response test on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 3 shows results of an abdominal tone test on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 4 shows results of a tail pinch test at 15 minutes on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 5 shows results of a tail pinch test at 30 minutes on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 6 shows results of a tail pinch test at 60 minutes on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 7 shows results of a tail pinch test at 120 minutes on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 8 shows results of a latency of the first mount test on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 9 shows results of a number of ejaculations test on rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 10 shows results of a test of the refractory period between the second ejaculation and the next mount for rats administered escalating doses of a preferred embodiment of a peptide according to the invention.

FIGURE 11 is a graphic representation of the effect of increasing concentrations of FG-005 peptide (QHNPK) on the number of mounts.

FIGURE 12 is a graphic representation of the effect of increasing concentrations of FG-005 peptide (QHNPR) on the number of mounts with intromission.

FIGURE 13 is a graphic representation of the effect of increasing concentrations of FG-005 peptide (QHNPR) on the number of mounts before the first ejaculation.

FIGURE 14 is a graphic representation of the effect of increasing concentrations of FG-005 peptide (QHNPR) on the number of mounts before the third ejaculation.

FIGURE 15 is a graphic representation of the effect of increasing concentrations of FG-005 peptide on the number of mounts before the fourth ejaculation.

FIGURE 16 is a graphic representation of the effect of increasing concentrations of FG-005 peptide on the mean number of mounts per ejaculation.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention relates to the field of psychopharmacology. More particularly, the invention relates to the treatment of DSM-III disorders, such as impaired interpersonal and behavioral disorders, including sexual disorders such as M.E.D. The patents and publications cited in this specification evidence the knowledge in this field and are hereby incorporated by reference in entirety. In the case of conflict between any teaching of a reference cited in this specification and any teaching specifically disclosed in this specification, the teaching specifically disclosed in this specification shall prevail.

The invention provides new therapeutic compositions and methods for treating DSM-III disorders, including M.E.D. The compositions and methods according to the invention provide improved awareness and alertness to environment, improved adaptation to environment and ability to sustain attention, and increased interest in environment and capacity for arousal, without increased aggressiveness. The present inventor has surprisingly discovered that peptides of the type disclosed in U.S. Patent No. 5,859,189 are effective as therapeutics for DSM-III disorders, including without limitation sexual disorders.

In a first aspect, the invention provides methods for treating DSM-III disorders. The methods according to the invention comprise administering to a mammal having a DSM-III disorder an amount of a peptide or a peptidomimetic according to the invention that is sufficient to reduce or eliminate symptoms of the DSM-III disorder.

For purposes of the invention, the term "mammal" is used in its usual taxonomic sense and specifically includes humans.

For purposes of the invention, a "peptide" is a molecule comprised of a linear array of amino acid residues connected to each other in the linear array by peptide bonds. Such linear array may optionally be cyclic, *i.e.*, the ends of the linear peptide or the side chains of amino acids within the peptide may be joined, *e.g.*, by a chemical bond. Such peptides according to the invention may include from about three to about 500 amino acids, and may further include secondary, tertiary or quaternary structures, as well as intermolecular associations with other peptides or other non-peptide molecules. Such intermolecular associations may be through, without limitation, covalent bonding (*e.g.*, through disulfide linkages), or through chelation,

electrostatic interactions, hydrophobic interactions, hydrogen bonding, ion-dipole interactions, dipole-dipole interactions, or any combination of the above.

Preferred peptides according to the invention comprise an amino acid sequence selected from the group consisting of:

Glp-His-Asn-Pro-Arg	[SEQ ID NO. 1]
Gln-His-Asn-Pro-Arg	[SEQ ID NO. 2]
Glp-His-Asn-Pro	[SEQ ID NO. 3]
Gln-His-Asn-Pro	[SEQ ID NO. 4],

wherein the sequences are shown in N to C configuration, and wherein Glp is pyroglutamate, Gln is glutamine, His is histidine, Asn is asparagine and Pro is proline.

Certain particularly preferred peptides according to the invention consist essentially of an amino acid sequence selected from the group consisting of:

Glp-His-Asn-Pro-Arg	[SEQ ID NO. 1]
Gln-His-Asn-Pro-Arg	[SEQ ID NO. 2]
Glp-His-Asn-Pro	[SEQ ID NO. 3]
Gln-His-Asn-Pro	[SEQ ID NO. 4],

wherein the sequences are shown in N to C configuration, and wherein Glp is pyroglutamate, Gln is glutamine, His is histidine, Asn is asparagine and Pro is proline.

Certain most preferred peptides according to the invention consist of an amino acid sequence selected from the group consisting of:

Glp-His-Asn-Pro-Arg	[SEQ ID NO. 1]
Gln-His-Asn-Pro-Arg	[SEQ ID NO. 2]
Glp-His-Asn-Pro	[SEQ ID NO. 3]
Gln-His-Asn-Pro	[SEQ ID NO. 4],

wherein the sequences are shown in N to C configuration, and wherein Glp is pyroglutamate, Gln is glutamine, His is histidine, Asn is asparagine and Pro is proline. In these peptides, by cyclization/decyclization, Glp and Gln interconvert.

In addition, certain preferred peptides according to the invention comprise, consist essentially of, or consist of an allelic variant of a peptide shown in any of SEQ ID NO. 1-4. As used herein, an "allelic variant" is a peptide having from one to two amino acid substitutions

from a parent peptide, but retaining the binding specificity and/or physiological activity of the parent peptide. As used herein, "retaining the binding specificity of the parent peptide" means being able to bind to a monoclonal antibody that binds to one of the peptides shown in SEQ ID NOS. 1-4 with an affinity that is at least one-tenth, more preferably at least one-half, and most preferably at least as great as that of one of the actual peptides shown in SEQ ID NOS. 1-4. Determination of such affinity is preferably conducted under standard competitive binding immunoassay conditions. "Retaining the physiological activity of the parent peptide" means retaining the ability of any one of the peptides shown in SEQ ID NOS. 1-4 to reduce or eliminate symptoms of a DSM-III disorder. Determining whether such symptoms are reduced or eliminated is further described later in this specification. The term "allelic variants" is specifically intended to include any human analogs of the peptides set forth in SEQ ID NOS. 1-4 which do not have the identical amino acid sequence thereof.

Peptides according to the invention can be conveniently synthesized using art recognized techniques (see *e.g.*, Merrifield, J. Am. Chem. Soc. 85: 2149-2154).

Preferred peptidomimetics retain the binding specificity and/or physiological activity of the parent peptide, as described above. As used herein, a "peptidomimetic" is an organic molecule that mimics some properties of peptides, preferably their binding specificity and physiological activity. Preferred peptidomimetics are obtained by structural modification of peptides according to the invention, preferably using unnatural amino acids, conformational restraints, isosteric replacement, cyclization. or other modifications. Other preferred modifications include without limitation, those in which one or more amide bond is replaced by a non-amide bond, and/or one or more amino acid side chain is replaced by a different chemical moiety, or any one of more of the N-terminus, the C-terminus or one or more side chain is protected by a protecting group, and/or double bonds and/or cyclization and/or stereospecificity is introduced into the amino acid chain to increase rigidity and/or binding affinity. All of these variations are well known in the art. Thus, given the peptide sequences disclosed herein, those skilled in the art are enabled to design and produce peptidomimetics having binding characteristics similar to or superior to such peptides (see *e.g.*, Horwell *et al.*, Bioorg. Med. Chem. 4: 1573 (1996); Liskamp *et al.*, Recl. Trav. Chim. Pays- Bas 1: 113 (1994); Gante *et al.*,

Angew. Chem. Int. Ed. Engl. 33: 1699 (1994); Seebach *et al.*, Helv. Chim. Acta 79: 913 (1996)).

As used herein, "having a DSM-III disorder" means manifesting at least one clinically observable behavior or physical characteristic that is generally recognized as a symptom of a DSM-III disorder. The term "to reduce or eliminate symptoms of a DSM-III disorder" means to obtain a clinically observable beneficial change in one or more behavior or physical characteristic that is generally recognized as a symptom of a DSM-III disorder. DSM-III disorders are diagnostic categories for which criteria are provided by a manual written by working groups of psychiatrists. This manual is published by the American Psychiatric Association, "Diagnostic and Statistical Manual of Mental Disorders", 1992, which is hereby incorporated by reference. Each of the disorders discussed below are well known, as evidenced by their treatment in this manual. Thus, only brief definitions are provided herein for the disorders discussed below.

In certain preferred embodiments, the DSM-III disorder is an avoidance disorder. As used herein, an "avoidance disorder" means a disorder having as an essential feature a pervasive pattern of social discomfort, fear of negative evaluation, and timidity. It includes excessive shrinking from contact with unfamiliar people.

In certain preferred embodiments, the DSM-III disorder is a decreased awareness disorder. As used herein, a "decreased awareness disorder" means a disorder marked by lack of awareness of the existence or feelings of others (e.g. treats a person like if he or she were a piece of furniture; does not notice another person's distress). These disorders can be elements of an autistic disorder.

In certain preferred embodiments, the DSM-III disorder is an attention deficit disorder. As used herein, an "attention deficit disorder" means a disturbance in which the predominant feature is the persistence of developmentally inappropriate and marked inattention.

In certain preferred embodiments, the DSM-III disorder is an arousal disorder. As used herein, an "arousal disorder" means a reactive attachment disorder such as persistent failure to initiate or respond to most social interactions. This can lead to severe forms in children that have been called "failure to thrive" or "hospitalism". Decreased interest in environment is another

element of reactive attachment disorders, commonly manifested as insufficient visual tracking of eyes, faces or voices, absence of reaching out to objects.

In certain preferred embodiments, the DSM-III disorder is impaired interpersonal functioning and relationship to the external world. As used herein, "impaired interpersonal functioning and relationship to the external world" means other interpersonal problems, examples of which are difficulties with co-workers or with romantic partners. These disorders include schizoid personality disorder, which is a pervasive pattern of indifference to social relationships and a restricted range of emotional experience and expression, and also include schizophrenia or depressive disorder.

In certain preferred embodiments, the DSM-III disorder is impaired social activity linked to sexuality. As used herein, "impaired social activity linked to sexuality" is impairment of social relationship to a sexual partner, which can lead to impairment of occupational functioning.

In certain preferred embodiments, the DSM-III disorder is impaired sexual behavior. As used herein, "impaired sexual behavior" includes hypoactive sexual desire disorder (H.S.D.D.), defined as persistently or recurrently deficient or absent sexual fantasies and desire for sexual activity, and further includes feelings of inadequacy concerning sexual performance such as untimely ejaculation.

In certain preferred embodiments, the DSM-III disorder comprises symptoms of more than one of these disorders.

In the methods according to the invention, the peptides or peptidomimetics according to the invention may be administered by any of a variety of means. In certain preferred embodiments, administration may be parenteral, most preferably intravenous. In other preferred embodiments, administration may be intranasal, oral, sublingual, transmucosal, intrarespiratory, or through an inert or iontophoretic patch.

Dosages of the peptide or peptidomimetic to be administered will depend on the particular patient, the condition, and the route of administration, and can be determined empirically by observing the reduction or elimination of symptoms of a DSM-III disorder in response to an elevating dosage regimen. Preferred dosages are from about 0.1 μg/kg to about 1

mg/kg, more preferably from about 1 μg/kg to about 100μg/kg, and most preferably from about 1 μg/kg to about 50 μg/kg.

In certain preferred embodiments, the peptide or peptidomimetic according to the invention is administered together with a second pharmaceutical agent, wherein the second pharmaceutical agent is present in an amount insufficient to reduce or eliminate symptoms of the DSM-III disorder, and wherein the peptide or peptidomimetic according to the invention and the second pharmaceutical agent act synergistically to reduce or eliminate symptoms of the DSM-III disorder. Administration of the peptide or peptidomimetic according to the invention and the second pharmaceutical agent can be simultaneous, sequential, or alternating. As used herein, a "pharmaceutical agent" is a substance other than food, water or air that mediates a beneficial physiological response at a sublethal concentration when administered to a mammal. Preferred second pharmaceutical agents include those currently used to treat DSM-III disorders, including M.E.D. "Synergistically" means that the peptide or the peptidomimetic and the second pharmaceutical agent together are more effective in reducing or eliminating symptoms of a DSM-III disorder than either one alone would be at the same concentration.

The methods according to the invention are useful for animal model studies of DSM-III disorders. The methods of the invention are also useful in treating mammals, including humans, for sexual disorders and other DSM-III disorders.

In a second aspect, the invention provides therapeutic compositions comprising a peptide or peptidomimetic according to the invention in an amount sufficient to reduce or eliminate symptoms of a DSM-III disorder in a mammal having the DSM-III disorder, and further comprising a pharmaceutically acceptable diluent and/or buffer and/or excipient.

According to this aspect of the invention, the terms "peptide", "peptidomimetic", and "to reduce or eliminate symptoms of the DSM-III disorder" are used as described for the first aspect of the invention. The terms "pharmaceutically acceptable", "diluent", "buffer" and "excipient" are used in their usual sense within the industry. The therapeutic composition may preferably be in the form of a solid, a liquid, a gel, an aerosol, or a sustained release formulation.

In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of an avoidance disorder. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of a decreased

awareness disorder. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of an attention deficit disorder. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of an arousal disorder. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of impaired interpersonal functioning and relationship to the external world. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of impaired social activity linked to sexuality. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of impaired sexual behavior. Each of these disorders are as defined for the first aspect of the invention. In certain preferred embodiments, the therapeutic composition is useful in preparing a medicament for the treatment of symptoms of more than one of these disorders.

In certain preferred embodiments, the peptide or peptidomimetic according to the invention is present in the therapeutic composition according to the invention together with a second pharmaceutical agent, wherein the second pharmaceutical agent is present in an amount insufficient to reduce or eliminate symptoms of the DSM-III disorder, and wherein the peptide or peptidomimetic according to the invention and the second pharmaceutical agent act synergistically to reduce or eliminate symptoms of the DSM-III disorder.

The therapeutic compositions according to the invention are useful for the preparation of medicaments, and are useful in the methods according to the invention.

The following examples are provided to further illustrate certain preferred embodiments of the invention and are not intended in any way to limit the scope of the invention.

Example 1

Synthesis of FG-005

The FG-005 peptide (QHNPR) was synthesized, for FGene by Bachem AG. The pentapeptide has a Glutamine at its N-terminal end which tends to transform (cyclization) into a pyroglutamate when in an aqueous phase but the peptide retains its biological properties. The synthesized peptide had a purity of more than 91% of its non-cyclic structure and 5% of its cyclic structure. It was conditioned under a neutral gas atmosphere (Argon) in vials of 500 µg to

be opened just prior to each experiment. Purity and structure were checked by HPLC and Mass Spectroscopy . Prior to injection, FG-005 was resuspended in a solution of Acetic acid 0.01N and PBS. Three concentrations were tested 0, 3, 15 and 30 µg/kg.

Example 2
Irwin test

An Irwin test was performed on 12 male Wistar rats (Iffa Credo, L'Arbresles, France), weighing 260-280 g. They were housed in groups of 4 in a climate controlled room with a 12h light:dark cycle (light 8:00 PM-8:00AM) and had access to food and water ad libitum. After a seven day acclimatization period, the rats were weighed, identified and randomly assigned to one of the four treatment groups. The drug was injected to the tail vein of the rats according to the group dose.

Observations were performed 15, 30, 60 and 120 minutes after administration. Among the most noticeable results are the results concerning the awareness state of the rats. As shown in Figure 1, rats are much more aware and alert to the environment and are much less likely to fall asleep after 2 hours of tests when injected with FG-005. Significant response to the wire maneuver test demonstrates improved adaptation to environment and ability to sustain attention. Their increased interest in environment and capacity for arousal is demonstrated by increased interest in the finger approach test, and increased vocalization when third parties approach. This increased alertness and vigilance is not associated with an increase of aggressiveness. Rats injected FG-005 are less stressed as shown by startle response test (Figure 2), and by the abdominal tone (Figure 3). They demonstrate less reactivity to nociceptive stimuli as shown by the tail pinch test (Figures 4, 5, 6, 7).

Example 3
Behavior of male rats in the presence of females

Behavior tests were performed on 12 male Wistar rats (Iffa Credo, L'Arbresles, France), weighing 260-280 g. They were housed in groups of 4 in a climate controlled room with a 12-h light:dark cycle and had access to food and water ad libitum. After seven days acclimatization period, the rats were weighed, identified and randomly assigned to one of the four treatment

groups. The rats were familiarized once with female rats which had been brought to sexual receptivity by injecting estradiol benzoate for 4 days (5 µg/0.5 ml oil, s.c. once daily). Behavioral testing was performed under blind conditions in a dimlight environment 2 hours after the onset of the dark phase of the light/dark cycle. Behavior was assessed by placing the male rat in a plexiglass cage (50 x 30 x 20 cm) five minutes before a receptive female was presented. All of the tests on rats were recorded on a VHS-videotape. The recorded parameters were: number of ejaculations, latency of first mount, latency of first ejaculation, number of mounts, postejaculatory interval, avoidance behavior patterns, awareness of other rats presence, initiation or response to social interaction, interest in other rat, self-care, willingness to enter into relationship. All of the quantitative results were analyzed using the Kruskal-Wallis test followed by the Mann-Whitney U-Test to compare each treated group with the control group. The statistical analyzes were carried out using the Statview 4.1 statistical package.

Example 4
Latency of the first mount

The VHS-video recorded study of the behavior of the rats showed that rats at a dose of 3 µg/kg exhibited a significantly increased latency of first mounts (see Table I and Figure 8). Treated rats are more aware of their partner's presence and considerably increase their signs of interest in the other rat. Social interaction and interpersonal activities before sexual intercourse are significantly increased.

TABLE I

	Number	Mean (sec.)	Std. Deviation	Std. Error	r
Control	3	8.333	2.887	1.667	
3 µg/kg	3	93.333	73.711	42.557	0.0238
15 µg/kg	3	23.000	10.440	6.028	0.6439
30 µg/kg	3	13.667	6.658	3.844	0.8657

Example 5
Ejaculations, self-care and interest in other rat

The number of episodes of intercourse (as measured by number of ejaculations in 45 minutes) are significantly increased (see Table II and Figure 9). After each penetration, rat's self-care, and attention to personal toilet is increased. After ejaculation non-treated rats lose interest in the other rat and stay at a distance in a self defeating attitude (digging into litter). In treated rats interest is maintained, with enhanced proximity of animals, decrease of fear of partner and improved ability to relate as shown by signs of tenderness and attention (muzzle to muzzle approach, licking), completely absent in non treated animals.

TABLE II

	Number	Mean	Std. deviation	Std. Error	r
Control	3	3.000	1.000	0.577	
3 µg/kg	3	5.333	0.577	0.333	0.0175
15 µg/kg	3	4.000	1.000	0.577	0.2367
30 µg/kg	3	4.667	1.155	0.677	0.0656

Example 6
Behavior during refractory periods

There was a loss of avoidance symptoms and enhanced willingness to enter into relationship during refractory periods, the duration of which is shortened (see Table III and Figure 10). Treated rats show a clear-cut improvement in willingness to enter into relationship with the other rat, increasingly respond to attempts of social interaction, completely loose the avoidance pattern behavior seen in control rats.

TABLE III

	Number	Mean (sec.)	Std. deviation	Std. Error	r
Control	3	467.333	87.763	50.670	
3 µg/kg	3	311.333	66.516	38.403	0.0476
15 µg/kg	3	412.000	87.430	50.478	0.4311
30 µg/kg	3	373.667	83.393	48.147	0.1981

Example 7
Dose-response relationship of FG-005 peptide on the male rat sexual behavior

Effect of increasing concentrations of FG-005 peptide (QHNPR) given i.v. on the number of sexual intercourse episodes of male rats with sexually receptive female, was assessed. All of the qualitative parameters were analyzed using one-way analysis of variance (ANOVA) for the differences between treated groups and followed by the multiple comparison test of Fisher (PLSD Fisher) to compare each group of FG-005-injected rats with the control group (vehicle-injected rats). Nine to ten rats were used for each group and P value of less than .005 was considered as significant for both tests.

At the doses of 0.03 µg – 1 µg and 3 µg/Kg, FG-005 peptide induced improvement on the male rat sexual behavior, during the 45-min-period of observation. This is appreciated by the significant dose-dependent increase of sexual interactions (mounts, mounts with intromission and mounts per ejaculation) during (first ejaculation latency and interejaculatory latency) episodes of sexual intercourse.

FG-005- treated rats exhibit a significant increase with a dose-dependent relationship of the total number of mounts with or without intromission, p= 0.0003 by ANOVA of 9-10 rats per dose (Figure 11 and Table IV); of the number of mounts with intromission, p= 0.0006 by ANOVA of 9-10 rats per dose (Figure 12 and Table V); of the number of mounts before the first ejaculation, p= 0.019 by ANOVA of 9-10 rats per dose (Figure 13 and Table VI); of the number of mounts during interejaculatory intervals, p= 0.017 by ANOVA of 9-10 rats per dose (Figure 14 and Table VII) and p= 0.025 by ANOVA of 6-10 rats per dose (Figure 15 and Table VIII);

and of the number of mount per ejaculation, p= 0.011 by ANOVA of 9-10 rats per dose (Figure 16 and Table IX).

As the number of sexual intercourse (mounts) increased before and during the ejaculatory intervals, parallely the first ejaculation latency of FG-005- treated rats increased significantly compared to vehicle – injected rats at the dose of 3 µg/ Kg (p= 0.03, n= 10 rats versus vehicle – injected rats, n= 10). And this is particularly appreciated by the significant dose-related prolongation of the second ejaculation latency, with a P value of 0.048 by ANOVA for 9- 10 rats per dose and a pronounced effect at 1 and 3 µg/ Kg. In the same way, the third ejaculation latency tended also to increase in a dose-related manner.

In this set of experiments, during the 45 min observation period, as the moments of social intercourse signs displayed by the male towards the female (sniffing, grooming, ano-genital exploration and mount) and of attention signs to personal toilet displayed by the male, are prolongated, and the total number of ejaculations of FG-005-treated rats tended to be diminished, and was lower than that of vehicle-treated rats at the dose of 3 µg/ Kg (p= 0.04, n= 10 rats per group).

In general, there was in FG-005-treated rats a loss of aggressive impulse behavior seen in control rats.

TABLE IV
Male rat sexual behavior with sexually receptive female
Dose-response relationship of Fg-005 peptide (OHNPR) (FIG. 11)

TABLE IVA

Recorded parameter: Number of mounts during the 45 min. observation period
Tableau d'ANOVA pour nomber total de montes

	DDL	Somme des carrés	Carré moyen	Valeur de F	Valeur de p
TT	3	13126.855	4375.618	8.076	.0003
Résidus	34	18421.356	541.805		

Modèle II estimation des composants de variance: 403.932

TABLE IVB

Tableau des Moyennes pour nombre total de montes
Effets: TT

	Nombre	Moy.	Dév. Std	Err. Std
Control	10	61.100	15.892	5.025
FG-0.3	9	81.778	26.729	8.910
Fg-1	9	96.667	24.027	8.910
FG-3	10	110.100	25.265	7.990

TABLE IVC

PLSD de Fisher pour nombre de montes
Effets: TT
Niveau de signif. 5%

	Ecart moyen	Ecart critique	Valeur de p
Control, FG-0.3	-20.678	21.735	.0615
Control, Fg-1	-35.567	21.735	.0021
Control, FG-3	-49.000	21.155	<.0001
FG-0.3, Fg-1	-14.889	22.299	.1838
FG-0.3, FG-3	-28.322	21.735	.0122
Fg-1, FG-3	-13.433	21.735	.2177

TABLE V
Male rat sexual behavior with sexually receptive female
Dose-response relationship of FG-005 peptide (ONRP) (FIG. 12)

Recorded parameter: Number of mounts with intromission

TABLE VA

Tableau d'ANOVA pour nombre total de montes avec pénétrations

	DDL	Sommes des carrées	Carré moyen	Valeur de F	Valeur de P
TT	3	10914.442	3638.147	7.379	.0006
Résidus	34	16764.111	493.062		

Modèle II estimation des composants de la variance: 331.368

TABLE VB

Tableau des Moyennes pour nombre total de montes avec pénétrations
Effets: TT

	Nombre	Moy.	Dév. Std	Dev. Std
Control	10	54.100	14.955	4.729
FG-0.3	9	77.111	23.945	7.982
Fg-1	9	90.556	26.735	8.912
FG-3	10	97.700	22.226	7.029

TABLE VC

PLSD de Fisher pour nombre total de montes avec pénétrations
Effets: TT
Niveau de signif. 5%

	Ecart moyen	Ecart critique	Valeur de p
Control, FG-0.3	-23.011	20.734	.0307
Control, Fg-1	-36.456	20.734	.0011
Control, FG-3	-43.600	20.181	.0001
FG-0.3, Fg-1	-13.444	21.273	.2077
FG-0.3, FG-3	-20.589	20.734	.0515
Fg-1, FG-3	-7.144	20.734	.4885

TABLE VI

Male rat sexual behavior with sexually receptive female
Dose-response relationship of FG-005 peptide (OHNPR) (FIG. 13)

Recorded parameter: Number of mounts before the first ejaculation

TABLE VIA

Tableau d'ANOVA pour nombre de montes avant la 1ère éjaculation

	DDL	Somme des carrés	Carré moyen	Valeur de F	Valeur de p
TT	3	3249.105	1083.035	3.789	.0190
Résidus	34	9717.211	285.800		

Modèle II estimation des composants de la variance: 83.997

TABLE VIB

Tableau des Moyennes pour nombre de montes avant la 1ère éjaculation
Effets: TT

	Nombre	Moy.	Dév. Std	Err. Std
Control	10	13.800	8.080	2.555
FG-0.3	9	31.111	20.368	6.789
Fg-1	9	33.444	16.356	5.452
FG-3	10	37.500	20.195	6.386

TABLE VIC

PLSD de Fisher pour nombre de montes avant la 1ère éjaculation
Effets: TT
Niveau de signif. 5%

	Ecart moyen	Ecart critique	Valeur de p
Control, FG-0.3	-17.311	15.786	.0326
Control, Fg-1	-19.644	15.786	.0162
Control, FG-3	-23.700	15.365	.0035
FG-0.3, Fg-1	-2.333	16.196	.7715
FG-0.3, FG-3	-6.389	15.786	.4165
Fg-1, FG-3	-4.056	15.786	.6050

TABLE VII
Male rat sexual behavior with sexually receptive female
Dose-response relationship of FG-005 peptide (OHNPR) (FIG. 14)

Recorded parameter: Number of mounts before the first ejaculation

TABLE VIIA

Tableau d'ANOVA pour nombre de montes avant la 3ème éjaculation

	DDL	Somme des carrés	Carré moyen	Valeur de F	Valeur de p
TT	3	894.889	298.296	3.939	.0166
Résidus	33	2499.111	75.731		

Modèle II estimation des composants de la variance: 24.079
Cas omis (manquants).

TABLE VIIB

Tableau des Moyennes pour nombre de montes avant la 3ème éjaculation
Effets: TT

	Nombre	Moy.	Dév. Std	Err. Std
Control	10	10.000	5.578	1.764
FG-0.3	9	13.444	5.918	1.973
Fg-1	9	18.333	9.849	3.283
FG-3	9	22.889	12.057	4.019

Cas omis (manquants).

TABLE VIIC

PLSD de Fisher pour nombre de montes avants la 3ème éjaculation
Effets: TT
Niveau de signif. 5%

	Ecart moyen	Ecart critique	Valeur de p
Control, FG-0.3	-3.444	8.135	.3952
Control, Fg-1	-8.333	8.135	.0450
Control, FG-3	-12.889	8.135	.0029
FG-0.3, Fg-1	-4.889	8.346	.2419
FG-0.3, FG-3	-9.444	8.346	.0278
Fg-1, FG-3	-4.556	8.346	.2748

Cas omis (manquants).

TABLE VIII
Male rat sexual behavior with sexually receptive female
Dose-response relationship of FG-005 peptide (OHNPR) (FIG. 15)

Recorded parameter: Number of mounts before the fourth ejaculation

TABLE VIIIA

Tableau d'ANOVA pour nombre de montes avant la 4ème éjaculation

	DDL	Sommes des carrés	Carré moyen	Valeur de F	Valeur de p
TT	3	865.087	288.362	3.665	.0246
Résidus	27	2124.590	78.689		

Modèle II estimation des composants de la variance: 27.387

7 cas omis (manquants).

TABLE VIIIB

Tableau des Moyennes pour nombre de montes avant la 4ème éjaculation
Effets: TT

	Nombre	Moy.	Dév. Std	Err. Std
Control	10	11.100	4.483	1.418
FG-0.3	8	11.500	3.338	1.180
Fg-1	7	19.143	6.256	2.365
FG-3	6	24.167	18.060	7.373

7 cas omis (manquants).

TABLE VIIIC

PLSD de Fisher pour nombre de montes avant la 4ème éjaculation
Effets: TT
Niveau de signif. 5%

	Ecart moyen	Ecart critique	Valeur de p
Control, FG-0.3	-.400	8.634	.9250
Control, Fg-1	-8.043	8.970	.0768
Control, FG-3	-13.067	9.399	.0082
FG-0.3, Fg-1	-7.643	9.430	.1075
FG-0.3, FG-3	-12.667	9.830	.0135
Fg-1, FG-3	-5.024	10.126	.3177

7 cas omis (manquants).

TABLE IX

Male rat sexual behavior with sexually receptive female
Dose-response relationship of FG-005 peptide (OHNPR) (FIG. 16)

Recorded parameter: mean number of mounts per ejaculation

TABLE IXA

Tableau d'ANOVA pour nombre de montes par éjaculation

	DDL	Somme des carrés	Carré moyen	Valeur de F	Valeur de p
TT	3	3149.935	1049.978	4.345	.0107
Résidus	34	8216.206	241.653		

Modèle II estimation des composants de la variance: 27.387

TABLE IXB

Tableau des Moy. pour nombre de montes par éjaculation
Effets: TT

	Nombre	Moy.	Dév. Std	Err. Std
Control	10	11.733	3.413	1.079
FG-0.3	9	20.220	12.976	4.325
Fg-1	9	26.911	18.092	6.031
FG-3	10	36.013	21.462	6.787

TABLE IXC

PLSD de Fisher pour nombre de montes par éjaculation
Effets: TT
Niveau de signif. 5%

	Ecart moyen	Ecart critique	Valeur de p
Control, FG-0.3	-8.487	14.515	.2430
Control, Fg-1	-15.178	14.515	.0409
Control, FG-3	-24.280	14.128	.0013
FG-0.3, Fg-1	-6.691	14.892	.3677
FG-0.3, FG-3	-15.793	14.515	.0339
Fg-1, FG-3	-9.102	14.515	.2112

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described

specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.